PEER REVIEW HISTORY

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis
AUTHORS	Ford, John; Shyangdan, Deepson; Uthman, Olalekan; Lois, Noemi; Waugh, Norman

VERSION 1 - REVIEW

REVIEWER	Sivaprasad, Sobha Moorfields Eye Hospital, Medical Retina
REVIEW RETURNED	01-Nov-2013

GENERAL COMMENTS	The network meta-analysis is very well written. The only point is that the study is focussing on 6 months data whilst there are published or about to be published RCT on 12 months data on triamcinolone and aflibercept. The study only included RCTs and therefore the authors could not analyse the open label extension of 12 months or more. Clinically, as central retinal vein occlusion is a chronic disease, it would be much more informative if a comparative analysis of data is possible for data beyond 6 months. The CRYSTAL study on ranibizumab for CRVO is a 24 months study but it is on-going.

REVIEWER	Shalchi, Zaid London Deanery
REVIEW RETURNED	11-Nov-2013

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. The authors are to be congratulated for an excellent systematic review that is well-designed and well-written overall. The authors consider an important and topical matter – which treatment is best for macular oedema in central retinal vein occlusion. As there are 2 current NICE-approved treatments (ranibizumab and dexamethasone), as well as several other non-licensed alternatives (bevacizumab, triamcinolone), this topic is of high relevance to clinicians. The need for this article is likely to increase further if and when aflibercept is approved by NICE for this indication.

	In general, the study seeks to answer a clear research question and uses a good and thorough search strategy to identify suitable articles in the literature. There is a logical and fair assessment of articles for inclusion and the results are well-presented and discussed. The findings of the study are rigorous. The authors do a good job of discussing the strengths and limitations of the work, and highlight the implications of the article for clinical care as well as future research. I think it presents data that is highly valuable to clinicians and warrants publication in a prominent journal like the BMJ. When is comes to comparing different treatments, high-quality systematic reviews typically discuss both efficacy AND safety – this is because more efficacious treatments can sometimes be associated with more adverse events. Unfortunately, this article only considers efficacy, and in this regard, makes the systematic review somewhat incomplete. The conclusions section of the abstract states "The anti-VEGFs are likely to be favored because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections." These statements are not justified as the article did not consider this aspect of the studies. To warrant publication in a journal like the BMJ, I feel there needs to be a rigorous assessment of the safety of each treatment. This need not be an onerous task as this data should be available from the included studies. It would also be useful clinically to know how often a treatment was given (eg number of injections in first 6 months) to achieve the visual acuity results outlined, as well as how many times patients were seen in an outpatient clinic. Please find below some more specific points with regard to certain sentences in the manuscript. Thank you again for asking me to review this article. I hope to see it in print in a revised version. Introduction: It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.(2) – Please clarify which population this refers to CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. – Although diabetes is a risk factor for CRVO, hypertension is a more significant risk factor and should be stated first Discussion

	This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines – do you mean confidence intervals? Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. – More aggressive in terms of what? It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab. – What does this mean?

VERSION 1 – AUTHOR RESPONSE

Dr Sivaprasad	
The network meta-analysis is very well written. The only point is that the study is focussing on 6 months data whilst there are published or about to be published RCT on 12 months data on triamcinolone and aflibercept. The study only included RCTs and therefore the authors could not analyse the open label extension of 12 months or more. Clinically, as central retinal vein occlusion is a chronic disease, it would be much more informative if a comparative analysis of data is possible for data beyond 6 months. The CRYSTAL study on ranibizumab for CRVO is a 24 months study but it is on-going.	We agree that it would be much better to have longer-term data, but because of the scarcity of that, we tried to make the best of what was available. Mixing 6 month and 12 month outcomes in the NMA would have substantially increased the methodological heterogeneity.
Dr Zaid Shalchi	
The authors are to be congratulated for an excellent systematic review that is well-designed and well-written overall. The authors consider an important and topical matter - which treatment is best for macular oedema in central retinal vein occlusion. As there are 2 current NICE-approved treatments (ranibizumab and dexamethasone), as well as several other non-licensed alternatives (bevacizumab, triamcinolone),this topic is of high relevance to clinicians. The need for this article is likely to increase further if and when aflibercept is approved by NICE for this indication.	No responses required, except to note that NICE have just issued guidance on aflibercept for CRVO – we were the ERG. It should also be noted that this paper was not a systematic review but an indirect comparison.
In general, the study seeks to answer a clear research question and uses a good and thorough search strategy to identify suitable articles in the literature. There is a logical and fair assessment of articles for inclusion and the results are well-presented and discussed. The findings of the study are rigorous. The authors do a good job of discussing the strengths and limitations of the work, and	No response required

highlight the implications of the article for clinical care as well As future research. I think it presents data that is highly valuable to clinicians and warrants publication in a prominent journal like the BMJ.	
When it comes to comparing different treatments, high-quality systematic reviews typically discuss both efficacy AND safety - this is because more efficacious treatments can sometimes be associated with more adverse events. Unfortunately, this article only considers efficacy, and in this regard, makes the systematic review somewhat incomplete. The conclusions section of the abstract states "The anti-VEGFs are likely to be favored because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections." These statements are not justified as the article did not consider this aspect of the studies. To warrant publication in a journal like the BMJ, I feel there needs to be a rigorous assessment of the safety of each treatment.	Safety was covered in another paper, which was a systematic review, published in BMJ Open (http://bmjopen.bmj.com/content/4/2/e004120.full). NB this study was not, as Dr Shalchi says, a systematic review. It was an indirect comparison of efficacy.
It would also be useful clinically to know how often a treatment was given (eg number of injections in first 6 months) to achieve the visual acuity results outlined, as well as how many times patients were seen in an outpatient clinic	Agreed that adding the number of injections would be helpful to readers. These have been included in the revised manuscript. Attendance at outpatient clinic is not described in the published literature.
It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.(2) - Please clarify which population this refers to.	This was based on a private census of about 5000 population aged 43-84 years in the Beaver Dam community in USA who were followed for 15 years (1987 to 2003) to calculate the cumulative incidence
CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. - Although diabetes is a risk factor for CRVO, >hypertension is a more significant risk factor and should be stated first	No response required
This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines - do you mean confidence intervals?	No, correct terminology in Bayesian analysis is credible intervals
Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. - More aggressive in terms of what?	AMD is aggressive with regards to the fact that there is a narrow window of opportunity to treat and to gain sight as a result of the treatment as CNVs tend to grow relatively fast. It is clear based on now very long term data that patients required pretty much life-long treatment.

It should be noted that during the appraisal of ranibizumab the evidence >review group found that in the cost-effectiveness analysis dexamethasone >was extendedly dominated by ranibizumab. - What does this mean? >	This will phrase will be explained
Dr Ryder	
Our statistical adviser made the following comments. it is very difficult to identify how many direct and indirect comparisons are being made. This might be due to their being little direct evidence comparing the treatments. In this situation, can we genuinely believe the robustness of the comparisons?	The reason for doing a network meta-analysis is because of the scarcity of direct head to head trials. We think those are required, but in their absence, an NMA is the best we can do and is what NICE asks for.
the consistency of the network (a fundamental assumption) is not checked	The network of evidence is star-shaped, it is not possible to access inconsistency of the network. All the trials compared active agents with placebo, there is no direct head-to-head trial. The aim of the network meta-analysis was to infer direct head-to-head efficacy because they are lacking.
the Bayesian approach should allow the treatments to be ranked following the met-analysis , but the authors don't do this	Actually we did it but dropped it from the final version, because we believe it did not add to the results. We would be happy to include it as supplementary online material if necessary.
the amount of heterogeneity is not discussed, and the choice of fixed or random effects meta-analysis model is not justified or explained in the results. In the discussion they say that methodological heterogeneity existed, and so it is strange that they don't clearly account for this in the analysis	<u>Fixed- versus random-effects model</u> DIC was considered in selecting the most parsimonious models. However, the evidence from DIC is inconclusive in choosing the best model, because the differences in DICs is less than 5. If difference in DIC is, less than 5, and the models make very different inferences, then it could be misleading just to report the model with the lowest DIC (reference: http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/dicpage.shtml). Fixed effect model was reported because it is strongly advised that better models should be guided by substantive theory, scientific plausibility and clinical relevance rather than automatic routine selection of model by Bayesian DIC. We have now clarified this in the method section "The fixed - effect model was chosen because of the small number of trials available for each comparison and difficulty in estimating between studies variance if random-effect model was implemented and the difference in DIC is less than 5" <u>Methodological heterogeneity</u> We could have explored the effect of potential sources of heterogeneity on the pooled treatment effect estimates from the NMA, however, we included only seven trials. To avoid over-fitting of

	data, a minimum trials-to-covariates ratio of 10 is required.
the authors talk about statistical significance, yet this is somewhat against the Bayesian framework they use; they should rather be talking about the probability of success, rather than p-values.	Thanks for pointing that out, we have now corrected this. All ‘statistically significant’ in the manuscripts have now been replaced with ‘more efficacious’. We did not report any p-values throughout the manuscript.